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<b>(54) Title:</b> MULTIPLE CONTROL STANDARD FOR BLOOD ANALYSIS  <b>(57) Abstract</b>  A multiple control standard for the use in the quality assurance of blood analysis instrumentation systems. The liquid control standard is able to act as a control standard for blood gas instrumentation systems measuring pH, pCO <sub>2</sub> and pO <sub>2</sub> of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and as a liquid control standard for ion selective electrode instrumentation systems for the measuring of electrolytes such as Na and K ions in the blood.		

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MULTIPLE CONTROL STANDARD FOR BLOOD ANALYSISBackground of the Invention

Clinical laboratories employ a variety of instrumentation systems for the analysis of patient samples. Frequently, three types of instruments are used to analyze particularly significant properties of fresh blood for diagnosis of respiratory-pulmonary ailments. These instruments are:

1. pH/blood gas instruments - measures blood pH,  $pCO_2$  and  $pO_2$ .
2. Co-oximeter instruments - measures total hemoglobin, oxyhemoglobin, carboxyhemoglobin and methemoglobin.
3. ISE Electrolyte instruments - measures electrolyte (such as sodium and, potassium) content of blood.

It is common practice to employ control solutions for verifying the accuracy and reliability of these instrumentation systems. A different control solution is used for each instrument. For example, a separate and distinct control solution is used to test the blood gas analyzer. A separate and distinct control solution is used to test the co-oximeter and a third separate and distinct solution is needed to test the ion analyzer. In other words, most pH/blood gas control materials serve as controls only for pH,  $pCO_2$  and  $pO_2$ . The blood gas controls that are formulated with hemoglobin solution or stabilized red blood cells do provide

control values for total hemoglobin in co-oximetry, but have no control values for either the other hemoglobin fractions or for electrolyte values.

05 Controls for hemoglobin fractions for use with co-oximetry instrumentation systems do not provide parameters for use as controls with pH/blood gas analyzers or for ISE electrolyte analyzers. Similarly, controls for ISE instrumentation are not useable for either pH/blood gas or co-oximetry  
10 instruments (in addition, some controls contain preservatives or other ingredients which make the material unsuitable for use in another type of instrument).

#### Summary of the Invention

15 This invention discloses a synthetic control solution which provides control parameters for three types of instrument systems: pH/blood gas, co-oximeters and ISE electrolytes instruments.

20 The synthetic liquid control is comprised of an aqueous solution buffered to a pH of from about 7.1 to 7.7 and containing sufficient bicarbonate ion to provide a  $pCO_2$  of from about 15 to about 80 after subsequently equilibrated with the desired levels of gaseous carbon dioxide, gaseous oxygen to provide a  
25  $pO_2$  of from about 50 to 400, retained dyes to provide measurements of several hemoglobin fractions and salts of ions to provide measurements of these ions in solution.

Detailed Description of the Invention

This invention discloses a synthetic liquid control standard comprised of an aqueous solution buffered to a pH of from about 7.1 to about 7.7 and  
05 containing sufficient bicarbonate ion to provide a  $pCO_2$  of from about 15 to about 80 after subsequently equilibrated with the desired levels of gaseous carbon dioxide, gaseous oxygen to provide a  $pO_2$  of from about 50 to about 400 retained, dyes to provide  
10 measurements of total hemoglobin and of several hemoglobin fractions, sodium and potassium salts to provide measurements of these ions in solution.

In order to provide the desired pH for the respective normal, acidosis or alkalosis conditions,  
15 a buffer material should be selected which has a  $pK_a$  close to the desired working pH. A particularly useful buffer material for providing the desired pH conditions in the control solution of this invention is N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic  
20 acid (HEPES) which has a  $pK_a$  of 7.31 at 37°C. Other suitable buffer materials are, for example, N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid (TES), which has a  $pK_a$  of 7.16 at 37°C.;  
25 3-(N-morpholino) propanesulfonic acid (MOPS), which has a  $pK_a$  of 7.01 at 37°C.; and Tri-(Hydroxymethyl) aminomethane (TRIS) which has a  $pK_a$  of 7.77 at 37°C. These and other such suitable buffer materials, including the sodium salt derivatives, are described by Good et al. Biochemistry 5, 467-77 (1966) and  
30 Ferguson et al., Analytical Biochemistry 104,

300-310 (1980), the teachings of which are hereby incorporated by reference.

The desired  $p\text{CO}_2$  level is provided in part by addition of bicarbonate ion, for example,  $\text{NaHCO}_3$ , to  
05 the aqueous solution that a  $p\text{CO}_2$  of from about 15 to about 80 is reached after subsequently equilibrated with the desired levels of gaseous carbon dioxide. The desired  $p\text{O}_2$  level of from about 50 to about 400 is facilitated by addition of gaseous oxygen to the  
10 solution or the head space in the receptacle containing the aqueous solution. Addition of gaseous carbon dioxide similarly can facilitate maintenance of the aforesaid desired  $p\text{CO}_2$  levels.

In a typical co-oximeter, a whole blood sample  
15 is aspirated into the instrument, mixed with diluent, hemolyzed, and brought to a constant temperature in a cuvette. A microcomputer calculates the total hemoglobin concentration present, expressed in grams per one hundred milliliters of  
20 whole blood g/dL THb. A typical co-oximeter also measures the percent oxyhemoglobin ( $\text{O}_2\text{Hb}$ ), carboxyhemoglobin (COHb), methemoglobin (MetHb), and reduced hemoglobin. Each of these species of  
hemoglobin will absorb light at different wave-  
25 lengths along the 500-650 nm range.

The control solution of the present invention contains absorbance means, such as dyes, which can absorb light in the 500-650 nm range at approximately the same percentage and wavelength as prede-  
30 termined concentrations of the different hemoglobin

species. By using this control solution with the co-oximeter, it can be determined whether or not the co-oximeter is functioning properly and whether or not the instrument needs to be recalibrated.

05       The absorbance means need not absorb light exactly as the different species of hemoglobin do. What is important is that a relationship can be determined such that the light absorbed by the absorbance means in the control solution can be  
10       correlated to a specific absorbance level of the particular hemoglobin species in question.

In a preferred embodiment, the control solution of the present invention contains a combination of Acid Red Dye #27 (CI 16185), Acid Yellow Dye #23 (CI  
15       19140) and Acid Blue Dye #9 (CI 42090). Also used is the combination of Ponceau 3R Red Dye (CI 16155) and Acid Blue Dye (CI 42090).

The blue dye is used because it has a maximum absorbance of light at 630nm as does methemoglobin.

20       The red dyes were chosen due to the fact that they show absorbance levels at the 560nm and 535nm wavelengths as does oxyhemoglobin, at the 570nm wavelength as does carboxyhemoglobin, and at the  
25       550nm wavelength as does reduced hemoglobin. By altering the concentrations of these dyes in the control solution, the control solution can simulate samples of blood having various levels of the different fractions of hemoglobin and of total hemoglobin.

Also contained within the control solution of this invention are predetermined amounts of electrolytes for testing ISE Electrolyte instruments. These electrolytes are placed into  
05 solution with constant ionic strength by dissolving the approximate amount of the salts of these electrolytes. The electrolytes most often tested are sodium and potassium ions. Therefore, controls having a measurable range of electrolyte values of  
10 Na and K can be made by the addition of appropriate quantities of sodium and potassium salts, such as NaCl and KCl.

In a preferred embodiment of this invention, the concentration of Na ions result from the  
15 combination of the salts of the acid dyes as well as the addition of NaOH, NaCl,  $\text{NaN}_3$  and  $\text{NaHCO}_3$ .

The density of the control solution can be placed at 1.01 to 1.03 and the viscosity of the solution from 2 to 4 centipoises which are similar  
20 to the density and viscosity of blood by adding up to 70 g/L of natural polymers, such as bovine serum albumin, or one of the synthetic polymers such as Polyethylene glycol (PEG) 8000, Polyvinylpyrrolidone (PVP) 40, Polyvinyl alcohol (PVA) and Ficoll 400.  
25 (Ficoll 400 is a synthetic high polymer made by the copolymerization of sucrose and epichlorohydrin produced by the Pharmacia Fine Chemicals AB Company of Uppsala, Sweden. Ficoll 400 indicates that the polymer has a molecular weight of approximately  
30 400,000.)



To ensure a stable long shelf life of more than two years at room temperature, a chemical preservative such as sodium azide or formaldehyde can be added to the solution, or the solution can be  
 05 sterilized by either membrane filtration or by high temperature sterilization if the solution does not contain the polymers used to increase the viscosity of the solution.

Two preferred formulations are listed below.  
 10 By varying the concentrations of the reagents in the following formulations a varied number of control standards can be produced. These control standards will then have different levels of pH, pCO<sub>2</sub>, pO<sub>2</sub>, total hemoglobin fractions and concentrations of  
 15 sodium and potassium ions.

#### Formulation I

	Compound	Concentration	
	HEPES and/or TRIS, MOPS	20	to 100 mM
	NaCl	40	to 100
20	KCl	2	to 8
	NaOH	0	to 60
	NaHCO <sub>3</sub>	18	to 26
	Acid Red Dye #27 (CI 16185)	2	to 5
	Acid Yellow Dye #23 (CI 19140)	3	to 7
25	Acid Blue Dye #9 (CI 42090)	0.015	to 0.08
	Polymer (PVA, Ficoll 400, PEG 8000, PVP 40 or Bovine serum albumin)	0	to 50 g/l

Formulation II

	Compound	Concentration	
	HEPES and/or TRIS, MOPS	20	to 100 mM
	NaCl	40	to 100
05	KCl	2	to 8
	NaOH	0	to 60
	NaHCO <sub>3</sub>	18	to 26
	NaN <sub>3</sub>	0	to 40
	Formaldehyde	0	to 60
10	Ponceau 3R Red Dye (CI 16155)	5	to 11
	Acid Blue Dye #9 (CI 42090)	0.015	to 0.08
	Polymer (PVA, Ficoll 400, PEG 8000 or Bovine serum albumin)	30	to 70 g/l

15        Using varying amounts of the reagents from the preferred formulations, three levels of multiple control standards can be formulated, namely Level I Control, Level II Control and Level III Control.

20        The multiple control standard of Level II simulates normal blood having a pH of about 7.4, a pCO<sub>2</sub> of about 40mm Hg and pO<sub>2</sub> of about 100mm Hg. The multiple control standard of Level II contains a sufficient concentration of dye to simulate a total hemoglobin concentration of about 14g/100ml of

25        blood. This total hemoglobin reading can be produced by placing red dye, yellow dye and blue dye

into solution to give the control standard the ability to absorb the light spectrum in the wavelengths between 400 to 650nm. The yellow dye is used in order to give the control the appearance of blood but does not absorb light in the critical  
05 ranges. A preferred concentration of dyes is about 3.5mM of Acid Red Dye #27 (CI 16185), about 5mM of Acid Yellow Dye #23 (CI 19140) and about 0.04mM of Acid Blue Dye #9 (CI 42090). This concentration of  
10 dyes in solution results in a control standard having an appearance of blood and giving a total hemoglobin reading of about 14 grams in 100ml of aqueous solution as measured by the Corning 2500 Co-oximeter, 9g/100ml by the IL282 Co-oximeter and  
15 26g/100ml by the ABL-30 Blood Gas Analyser. The multiple control standard of Level II also contains a concentration of sodium ions of about 140mM and a concentration of potassium ion of about 5mM.

The multiple control standard of Level I  
20 simulates blood having a low pH of 7.10 to 7.20, a high  $pCO_2$  of from about 60 to 70mm Hg, and a low  $pO_2$  of from about 50 to 65mm Hg. (This control standard thus simulates acidosis.) The control standard of Level I also contains a low concentration of Na ions  
25 from about 115 to 125mM and a low concentration of K ions from about 2.5 to 3.5mM.

The multiple control standard of Level I also contains a lower concentration of all dyes to simulate a total hemoglobin of about 9g/100ml of  
30 blood as read by the Corning 2500 Co-oximeter. A

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preferred control solution of Level I contains about 2mM of Acid Red Dye #27 (CI 16185), about 3mM of Yellow Dye #23 (CI 19140), and about 0.015 mM of Acid Blue Dye #9 (CI 42090).

05       The multiple control standard of Level III simulates a sample of blood having a high pH of about 7.6, a low  $p\text{CO}_2$  of about 22mm Hg and a high  $p\text{O}_2$  level of about 150mm Hg. (This control standard thus simulates alkalosis). The multiple control  
10       standard of Level III also contains a sufficient concentration of dye to simulate a high total hemoglobin of about 18g/100ml of solution. This total hemoglobin reading is produced by having a higher concentration of all dyes, preferably about  
15       5mM of Acid Red Dye #27 (CI 16185), about 7mM of Acid Yellow Dye #23 (CI 19149), and about 0.08mM of Acid Blue Dye #9 (CI 42090). The control standard of Level III also contains a higher concentration of sodium ions 160mM and of potassium ions of about  
20       7mM.

      The desired  $p\text{CO}_2$  value is provided in part by the addition of bicarbonate ion, e.g.  $\text{NaHCO}_3$  to the aqueous solution.  $\text{CO}_2$  gas is then added to the aqueous solution until a  $p\text{CO}_2$  of from about 15 to  
25       about 80mm Hg is attained, depending upon which control level is being produced.

      The desired  $p\text{O}_2$  level of from about 50 to 160mm Hg, depending upon which control level is being produced, is reached by the addition of gaseous  
30       oxygen to the solution and head space in the

receptacle containing the aqueous solution. Addition of gaseous carbon dioxide similarly can facilitate maintenance of the aforesaid desired  $p\text{CO}_2$  levels.

05       The final control standard solution is retained in a sealed or air-tight receptacle such as, for example, a glass vial or ampule to retain the desired gas equilibrium. The head space in the receptacle can be filled with an appropriate gas to  
10 facilitate the provision of the aforesaid  $p\text{CO}_2$  conditions. For example, for the acidosis blood gas control, a mixture of 65% oxygen, 5.9% of carbon dioxide and 87.6% of nitrogen is used. For the  
15 normal blood gas control a mixture of about 4.1% of carbon dioxide, 11.8% of oxygen and 84.1% of nitrogen is used. For the alkalosis blood gas control a mixture of about 2.3% of carbon dioxide, 18% of oxygen and 79.7% of nitrogen is used. It  
20 will be appreciated that any other inert gas can be used as a substitute for part or all of the nitrogen portion of the head space in the foregoing illustrative examples.

      The following specific and detailed example will further illustrate the invention although it  
25 will be appreciated that this example is not meant to restrict the invention to the specific details found in such example.

EXAMPLE

The blood gas control liquids are preferably formulated to represent three levels of pH,  $\text{PCO}_2$  and  $\text{PO}_2$  values to have different combinations of dye concentration that simulate three levels of hemoglobin values and the visual appearance of hemolyzed blood plus three different levels of both sodium and potassium ions.

A preferred embodiment of the invention has the following formulation:

	<u>COMPOUND</u>	<u>CONCENTRATION</u>
	HEPES	40 mM
	NaCl	40 to 100 mM
	KCl	2 to 8 mM
15	NaOH	20 to 30 mM
	$\text{NaHCO}_3$	

Three different buffers were made using HEPES, NaOH, NaCl, KCl and  $\text{NaHCO}_3$  in different concentrations. They were:

	<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
20			
	HEPES 40.0 mM	40.0 mM	40.0 mM
	NaOH 20.0	25.7	29.6
	KCl 3.0	5.0	7.0
	NaCl 73.2	81.5	99.3
25	$\text{NaHCO}_3$ 21.3	23.9	19.4

Three different levels of dyes were added to the corresponding buffer solutions.

	<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
Red			
30	Dye #27 2.34 mM	3.72 mM	4.84 mM

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Yellow

Dye #23	1.57	2.6	3.39
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Blue

Dye #9	0.016	0.04	0.08
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05        The buffered dye solutions were then separately placed in a container which was thermally controlled to 25°C. The appropriate gas mixture was then bubbled through each solution at a rate of 5 to 7 L/min. until the pH, PCO<sub>2</sub> and PO<sub>2</sub> reached

10 equilibrium values, as determined by appropriate blood gas analyzers. The gas mixtures used had the following compositions:

	<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
CO <sub>2</sub>	6.5%	4.1%	23%
15 O <sub>2</sub>	5.9	11.8	18.0
N <sub>2</sub>	87.6	84.1	79.7

After equilibrium was reached, the gaseous solution was subdivided into 2.6 ml quantities and placed into 3ml glass ampules which had been purged

20 with the same gas mixture used in bringing the solution to equilibrium. The filled ampules were heat-sealed.

The control liquid had an appearance of a hemoglobin solution and showed the corresponding

25 hemoglobin value equivalents as the following table:

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	THb	O <sub>2</sub> Hb%	O <sub>2</sub> SAT%	COHb%	MethHb%	O <sub>2</sub> Ct	Vol%O <sub>2</sub>
<u>ACIDOSIS (I)</u>							
Corning 2500	9.0g±0.5g/ 100 ml		-43±3	70±5	63±5	-5.3±0.3	
IL 282	5.5±0.5	-38±3		112±5	0.9±0.2		-2.9±0.3
<u>Normal (II)</u>							
Corning 2500	14.±0.5		-40±3	65±5	64±5	-7.5±0.4	
IL 282	8.8±0.5	-35±3		101±5	6.9±0.5		-4.2±0.3
<u>Alkalosis (III)</u>							
Corning 2500	18±0.5		-39±3	64±5	64±5	-9.4±0.4	
IL 282	11.5±0.5	-32±3		93±5	11.9±0.5		-5.0±0.3



The formulated liquid also had three levels of concentration of sodium and potassium as measured by the following different models of ion selective electrode instrumentation:

		<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
05	Na			
	Corning 902	120±3mM	140±3mM	165±4mM
	614	120±3mM	140±3mM	165±4mM
	Nova - 1	120±3mM	140±3mM	160±4mM
10	IL-501	120±3mM	140±3mM	160±4mM
	K			
	Corning 902	3.0±0.3mM	5.0±0.3mM	7.4±0.4mM
	614	3.0±0.3mM	5.0±0.3mM	7.4±0.4mM
	Nova - 1	3.0±0.3mM	5.0±0.3mM	7.0±0.4mM
15	IL-501	3.0±0.3mM	5.0±0.3mM	7.0±0.4mM

The ampuled formulated liquid has the corresponding values of pH,  $\text{PCO}_2$  and  $\text{PO}_2$  for the blood gas analyzers.

		<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
20	pH (unit)	7.15 (7.10-7.20)	7.4 (7.38-7.42)	7.6 (7.58-7.62)
	$\text{PCO}_2$ mm Hg	70 (66-72)	40 (38-42)	22 (20-24)
	$\text{PO}_2$ mm Hg	60 (58-67)	102 (100-104)	150 (145-155)

Those values were measured at 37°C.

The ampules containing formulated liquid can be  
 25 heat sterilized at 15' PSI for 30 minutes for long term shelf life.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific  
05 embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

For example, it will be understood by one having ordinary skill in the art that other dye  
10 combinations can be used which can absorb light as hemoglobin does. This invention is not limited to the illustrated examples of dye combinations.

Claims

1. A multiple liquid control standard for use in the quality assurance of blood analysis instrumentation systems, said liquid control  
05 standard being able to act as a control standard for blood gas instrumentation systems measuring pH,  $pCO_2$  and  $pO_2$  of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the  
10 blood and the relative amounts of other hemoglobin fractions present in the blood, and as a control standard for ion selective electrode instrumentation systems measuring the concentration of electrolytes in the blood.
- 15 2. A multiple liquid control standard as recited in Claim 1, wherein the control standard is an aqueous solution buffered by a buffering agent to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ions to  
20 provide a  $pCO_2$  from about 15 to about 80mm Hg, gaseous oxygen to provide a  $pO_2$  of from about 50 to about 400mm Hg retained, absorbance means to provide a control test which corresponds to a predetermined level of hemoglobin and hemo-  
25 globin fractions, and salts of electrolytes to provide a control test for a corresponding ion selective electrode system.

3. A multiple liquid control standard as recited in Claim 2, wherein the buffering agent is selected from the group consisting of  
05 N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid, 3-(N-morpholino) propane sulfonic acid and tri-(hydroxymethyl) amino methane.
4. A multiple liquid control standard as recited in Claim 2, wherein the absorbance means is comprised of Acid Red Dye #27 (CI 16185), and  
10 Acid Blue Dye #9 (CI 42090).
5. A multiple liquid control standard as recited in Claim 2, wherein the absorbance means is comprised of Ponceau 3R Red Dye (CI 16155) and Acid Blue Dye #9 (CI 42090).
- 15 6. The liquid control standard as recited in Claim 2, wherein said liquid control standard contains a predetermined concentration of Na and K ions so that the control standard can be used to test an ion selective electrode instrumentation system which measures the amount of Na  
20 and K ions present in blood.
7. A multiple liquid control standard as recited in Claim 2, wherein the density of said control standard is about from 1.01 to 1.03 and the  
25 viscosity of said control standard is about from 2 to 4 centipoises.

8. A multiple liquid control standard as recited in Claim 7, wherein the density and the viscosity of said control standard are adjusted by a polymer selected from the group consisting of Bovine serum albumin, Polyethylene glycol 8000, Ficoll 400, Polyvinylpyrrolidone 40, and Polyvinyl alcohol.  
05
9. A multiple liquid control standard as recited in Claim 2, wherein the pH ranges from about 7.10 to 7.20, the  $pCO_2$  ranges from about 60 to 70mm Hg, the  $pO_2$  ranges from about 50 to about 65mm Hg, the Na ion concentration ranges from about 115 to about 125 mM, the K ion concentration ranges from about 2.5 to about 3.5 mM and the absorbance means simulates blood having a low level of total hemoglobin.  
10  
15
10. A multiple liquid control standard as recited in Claim 9, wherein the absorbance means is comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090).  
20
11. A multiple liquid control standard as recited in Claim 9, wherein the absorbance means is comprised of Ponceau Red Dye 3R (CI 16155) and Acid Blue Dye #9 (CI 42090).
- 25 12. A multiple liquid control standard as recited in Claim 2, wherein the pH ranges from about

05 7.35 to 7.45, the  $p\text{CO}_2$  ranges from about 35 to 45mm Hg; the  $p\text{O}_2$  ranges from about 95 to about 110mm Hg, the Na ion concentration ranges from about 135 to about 145 mM, the K ion concentration ranges from about 4.5 to about 5.5 mM and the absorbance means simulates blood having a normal level of total hemoglobin.

10 13. A multiple liquid control standard as recited in Claim 12, wherein the absorbance means is comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090).

15 14. A multiple liquid control standard as recited in Claim 12, wherein the absorbance means is comprised of Ponceau Red Dye 3R (CI 16155) and Acid Blue Dye #9 (CI 42090).

20 15. A multiple liquid control standard as recited in Claim 2, wherein the pH ranges from about 7.55 to 7.65, the  $p\text{CO}_2$  ranges from about 15 to 25mm Hg, the  $p\text{O}_2$  ranges from about 140 to about 160mm Hg, the Na ion concentration ranges from about 150 to about 170 mM, the K ion concentration ranges from about 6.5 to about 7.5 mM and the absorbance means simulates blood having a high level of total hemoglobin.

25 16. A multiple liquid control standard as recited in Claim 15, wherein the absorbance means is

comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090).

17. A multiple liquid control standard as recited in Claim 15, wherein the absorbance means is comprised of Ponceau Red Dye 3R (CI 16155) and Acid Blue Dye #9 (CI 42090).
18. A multiple control standard for use in the quality assurance of blood analysis instrumentation systems, said liquid control standard being able to act as a control standard for blood gas instrumentation systems measuring pH,  $pCO_2$  and  $pO_2$  of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and a control standard for ion selective electrode instrumentation systems measuring the concentration of Na and K ions in the blood, wherein the control standard is an aqueous solution buffered by a buffering agent to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ion to provide a  $pCO_2$  from about 15 to about 80mm Hg, gaseous oxygen to provide a  $pO_2$  of from about 50 to about 400mm Hg retained, absorbance means to provide a control test which corresponds to a predetermined level of hemoglobin and

hemoglobin fractions, said absorbance means being comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090), and salts of Na and K to provide a control test for a  
05 corresponding ion selective electrode instrumentation system.

19. A multiple control standard for use in the quality assurance of blood analysis instrumentation systems, said liquid control standard  
10 being able to act as a control standard for blood gas instrumentation systems measuring pH,  $\text{pCO}_2$  and  $\text{pO}_2$  of blood, as a control standard for a co-oximeter measuring the amount of total  
15 hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and a control standard for ion selective electrode instrumentation systems measuring the concentration of Na and K  
20 ions in the blood, wherein the control standard is an aqueous solution buffered by a buffering agent to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ion to provide a  $\text{pCO}_2$  from about 15 to about 80mm Hg,  
25 gaseous oxygen to provide a  $\text{pO}_2$  of from about 50 to about 400mm Hg retained, absorbance means to provide a control test which corresponds to a predetermined level of hemoglobin and hemoglobin fractions, said absorbance means being  
30 comprised of Ponceau 3R Red Dye (CI 16155) and Acid Blue Dye #9 (CI 42090).



# INTERNATIONAL SEARCH REPORT

International Application No **PCT/US87/00796**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>3</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC: <b>GOIN/3100</b> ; <b>US: 436/11</b>		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>4</sup>		
Classification System	Classification Symbols	
US	436/11-18	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>5</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup>		
Category <sup>*</sup>	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>
A	US,A, 4,485,174, Published 27 Nov. 1984, (Chiang et al.)	1-19
A	US,A, 4,469,792, Published 04 Sept. 1984, (Simmonds et al.)	1-19
A	US,A, 4,458,021, Published 03 July 1984, (Herring.)	1-19
A	US,A, 4,163,734, Published 07 Aug. 1979, (Sorensen et al.)	1-19
Y	US,A, 4,279,775, Published 21 July 1981, (Louderback et al.).	1-19
Y	US,A, 4,369,127, Published 18 Jan. 1983, (Cormier et al.).	1-19
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p><sup>*</sup> Special categories of cited documents: <sup>15</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search <sup>1</sup>		Date of Mailing of this International Search Report <sup>2</sup>
26 June 1987		10 JUL 1987
International Searching Authority <sup>1</sup>		Signature of Authorized Officer <sup>20</sup>
ISA/US		T. J. Wallen